REMARKS

Claims 1-21 are currently pending in the application. As a result of the restriction requirement, claims 1-12 and 18-20 were withdrawn from consideration. Claims 13-17 are being examined on their merits. Claim 21 is newly added.

AMENDMENTS TO THE SPECIFICATION

The specification was amended at page 6, line 27, to correct an obvious typographical error. The amendment to the specification is supported by the as-filed application and does not add new matter. Applicants therefore request entry of this amendment.

AMENDMENTS TO THE CLAIMS

Claim 13 was amended to add "wild-type" (see specification page 25 lines 15-16 for support); delete the phrase "resulting from an alteration in APAF1"; and add "the step of testing the drug candidate in a depression model" (see specification page 53, lines 10-20 for support). Claims 15 and 16 were amended to correct obvious typographical errors. New claim 21 was added to specify that the biological activity is apoptosome activation. All of these amendments are supported by the as-filed application and do not constitute the addition of new matter. Applicants therefore request their entry.

Objections to the Specification and Claims

As set forth on page 2 of the outstanding Office Action, the disclosure and the claims were objected to because of a list having two "(f)"mutations. The claims and specification were amended to correct this obvious typographical error. Applicants therefore request withdrawal of this objection.

Claims Rejections Under 35 USC § 112, Second Paragraph

As set forth on pages 2-3 of the outstanding Office Action, claims 13-17 are rejected under 35 USC § 112 for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

More specifically, it is alleged that with respect to claim 13 that "it is not clear what the alteration in APAF1 gene is that results in depression." It is further alleged that it is not clear if the homolog is the mutant form of APAF1, or if the homolog has a mutation corresponding to that in APAF1. Applicants respectfully traverse this rejection.

Applicants note that the specification clearly indicates that the inventors have identified APAF1 as a depression related gene. More specifically, the inventors have identified variants of APAF1 associated with a predisposition to depression. Example 1 describes how APAF1 variants were associated with depression (see specification, at page 56, line 12 through page 57, line 26). Example 2 in the specification (see specification page 57, line 28, through page 58, line 18) clearly indicates that altered APAF1 bioactivity is associated with predisposition to depression. Based on these findings, Applicants are claiming a method for screening for depression therapeutics that modulate APAF1 bioactivity, *e.g.*, lower apoptosome activation.

The specification also indicates that a number of different APAF1 related bioactivities can be screened. Example 2 describes a caspase activation assay (see specification, page 57, line 28, through page 58, line 18). Example 3 describes numerous APAF1 based configurations for a primary apoptosome assay (see specification, page 58, line 20 through page 59, line 3). Example 3 describes that compounds which reduce caspase activation in the apoptosome reconstitution assay are potential depression therapeutics. Example 3 indicates that wild-type or mutant APAF1 can be used in these assays. Example 4 describes an APAF1 oligomerization assay for identifying depression therapeutics (see specification, page 59, line 25).

A variety of other assays are described in the specification such as yeast two-hybrid assays and protein-protein interaction assays for identifying depression therapeutics. Page 25, lines 15-25 of the specification relates that the depression therapeutics can be screened for by using wild-type APAF1, mutant APAF1 polypeptide, and APAF1 homologs from any organism including, *C. elegans* and *Drosophila*, as well as humans. Given that numerous APAF1 variants as well as their bioactivities are disclosed in the specification along with how to screen these activities (as well as actual

results from apoptosome reconstitution/caspase activation assays), Applicants respectfully request withdrawal of this rejection.

Claims Rejections Under 35 USC § 112, First Paragraph

As set forth on pages 3-4 of the Office Action, claims 13-17 are rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

Several allegations were made in the Office Action to support the written description rejection. First, it was alleged that the specification describes drug screening on pages 25-37, but does not describe mutant APAF1, homologs, derivatives or fragments thereof having an activity, or an activity that could be blocked that would aid in the treatment of depression. Second, it was alleged that the dependent claim lists several mutations, but nowhere in the specification has the activity of these mutant APAF1 polypeptides been explored. Applicants respectfully submit that contrary to these allegations, the specification describes mutant APAF1, homologues, derivatives or fragments thereof having an activity, or an activity that could be blocked that would aid in the treatment of depression.

Specifically, Applicants note that Example 2 describes the biological activity of a number of APAF1 mutants, the results of which are summarized in FIGS. 1-3. In particular, these APAF1 mutants activate caspase-9 activity in apoptosome reconstitution assays. Applicants have described in the as-filed specification a number of APAF1 mutants, homologs, derivatives and fragments of APAF1 that have an activity which can be assayed for identifying potential depression therapeutics. For example, the as-filed specification, at pages 57-58 discloses the biological activity of APAF1 variants having the following amino acid substitutions C450W, E777K, N782T, and Q465R. Furthermore, there are also a number of art-known homologs, variants, and derivatives of APAF1 as acknowledged in the instant Office Action (page 4). Applicants have described in the as-filed application a number of art-known assays that can be used for determining APAF1 bioactivity including apoptosome based assays (see e.g., specification, Examples 2-3, pages 57-59), protein-protein interaction assays (see e.g.,

specification, pages 28-33), assays for ATP binding (see e.g., specification, pages 25 lines 29-33), and assays for disruption of cytochrome c binding (see e.g., specification, pages 25 lines 29-33). The specification clearly discloses numerous APAF1 variants that have measurable biological activities and the assays that can be used to detect these activities. Applicants therefore respectfully request withdrawal of this rejection.

CONCLUSION

It is not believed that any time extension or fees are required with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency or credit any overpayment to Deposit Account no. **50-1627**.

Respectfully submitted,

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